

## CORRECTED VERSION

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
11 November 2004 (11.11.2004)

PCT

(10) International Publication Number  
**WO 2004/096208 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 31/36**,  
47/10, 47/12, 47/14, 47/32, 47/34, 47/38, 47/42, 47/44,  
9/14, 9/16, 9/48, 9/52, A61P 25/22, 25/24 // C07D 407/12

[JP/JP]; c/o MITSUBISHI PHARMA CORPORATION,  
Tokyo Office, 2-6, Nihonbashi-honcho 2-chome, Chuo-ku,  
Tokyo 103-8405 (JP).

(21) International Application Number:  
PCT/JP2004/005864

(74) Agent: **TAKAYANAGI, Masau**; Mitsubishi Pharma  
Corporation, Intellectual Property Department, 2-6, Ni-  
honbashi-honcho 2-chome, Chuo-ku, Tokyo 103-8405  
(JP).

(22) International Filing Date: 23 April 2004 (23.04.2004)

(25) Filing Language: English

(81) Designated States (unless otherwise indicated, for every  
kind of national protection available): AE, AG, AL, AM,  
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,  
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,  
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,  
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,  
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,  
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,  
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,  
ZW.

(26) Publication Language: English

(30) Priority Data:  
2003-121339 25 April 2003 (25.04.2003) JP

(71) Applicant (for all designated States except US): MIT-  
SUBISHI PHARMA CORPORATION [JP/JP]; 6-9,  
Hiranomachi 2-chome, Chuo-ku, Osaka-shi, Osaka  
541-0046 (JP).

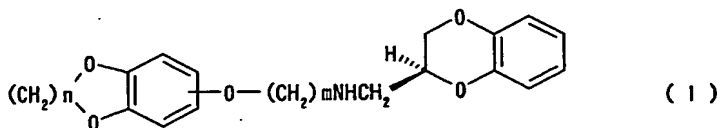
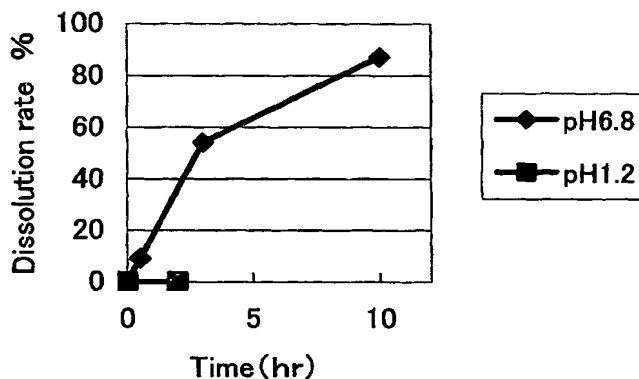
(72) Inventor; and

(75) Inventor/Applicant (for US only): **SUZUKI, Tetsuya**

(84) Designated States (unless otherwise indicated, for every  
kind of regional protection available): ARIPO (BW, GH,  
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),

[Continued on next page]

(54) Title: COMPOSITION FOR ORAL ADMINISTRATION CONTAINING ALKYLENE DIOXYBENZENE DERIVATIVE



(57) Abstract: The present invention relates to a composition for oral administration containing an alkylenedioxybenzene derivative represented by the general formula (I): (wherein m represents an integer of 2 to 5, and n represents an integer of 1 to 3) or an acid addition salt thereof, which allows for duration of the drug concentration in plasma. By dispersing a compound represented by the general formula (I) in a matrix containing a synthetic polymer and/or waxes, a safe and useful pharmaceutical preparation for oral administration having the stable drug releasing property in a living body was obtained.



Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

— *with international search report*

**(48) Date of publication of this corrected version:**

17 November 2005

**(15) Information about Correction:**

see PCT Gazette No. 46/2005 of 17 November 2005, Section II

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

## DESCRIPTION

### COMPOSITION FOR ORAL ADMINISTRATION CONTAINING ALKYLENE DIOXYBENZENE DERIVATIVE

#### Technical Field

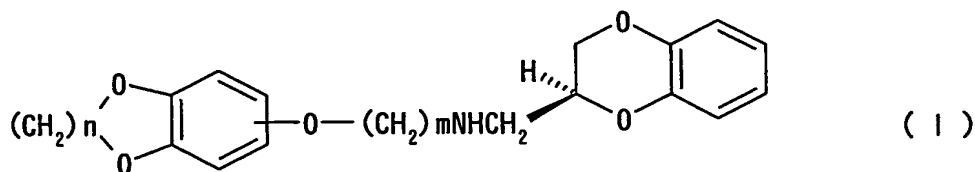
The present invention relates to a composition for oral administration which releases a drug at a controlled releasing rate when orally administered.

#### Background Art

Generally, the drug concentration in blood is used as one index of drug efficacy, undesirable reaction (side effect, allergic reaction, excessive reaction), and many examples are reported in which occurrence of an undesirable reaction depends on the drug concentration in blood. In order to avoid these undesirable reactions and improve QOL of a patient, it is essential to control the drug concentration in blood.

When dose dependency is observed between the drug concentration in blood and a undesirable reaction, prolongation/regulation of release of a drug from a drug preparation is frequently performed in order to alleviate an undesirable reaction. Design of these regulated/prolonged release compositions and techniques of controlling a releasing rate have been developed by those skilled in the art for a few decades, and are well-known in the art (L. Krowczynski, Extended Release Dosage Forms, CRC-Press Inc., USA, 1987).

An alkylenedioxybenzene derivative represented by the general formula (I):



(wherein m represents an integer of 2 to 5, and n represents an integer of 1 to 3)

or an acid addition salt is a compound which has the strong affinity for a 5-HT<sub>1A</sub> receptor, and is expected as a drug for treating anxiety, for manic-depressive psychosis (US Patent 5,168,099).

When a conventional preparation (a tablet using D-mannitol as an excipient, sodium carboxymethylstarch as a disintegrating agent, and hydroxypropylcellulose as a binder) of 5-[3-[[[(2S)-1,4-benzodioxan-2-ylmethyl]amino]propoxy]-1,3-benzodioxole hydrochloride (hereinafter, referred to as MKC-242 in some cases in the present specification) which is

one of an alkylendioxybenzene derivative represented by the general formula (I) or an acid addition salts is administered to a human, symptoms such as nausea, dizziness, orthostatic syncope and the like are recognized although they are all slight, and it has been found that these undesirable symptoms occur depending on the drug concentration in plasma. In addition, a half-life  $T_{1/2}$  is as short as 2 to 5 hours, and the drug concentration in plasma does not last.

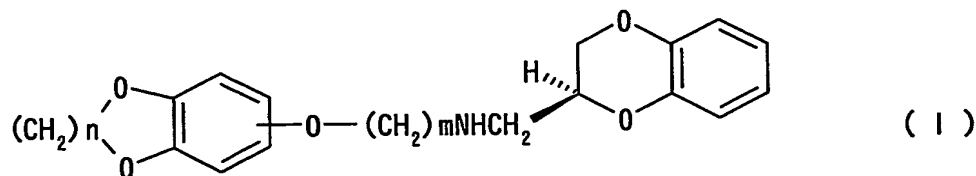
On the other hand, the solubility of a drug is pH-dependent and, in view of the physical and physiological environment in a digestive tract of a human and a digestive tract moving time of a preparation, it is considered that an alkylendioxybenzene derivative is not suitable for an oral regulated/prolonged release dosage form.

An object of the present invention is to overcome these problems of kinetics in a living body and pharmacological activity or physicochemical drawbacks possessed by an alkylendioxybenzene derivative or an acid addition salt thereof, and provide a composition for oral administration in which the drug concentration is not rapidly increased in plasma, and the drug concentration in plasma can be maintained over a long period of time.

### Disclosure of Invention

The present inventors found that the problems can be solved by dispersing a compound of the general formula (I) in a matrix material, or coating a composition containing the compound of the general formula (I) with an enteric film, or combining both of them.

The present invention relates to a composition for oral administration which releases a drug at a controlled releasing rate when orally administered. That is, the present invention provides a composition for oral administration which suppresses rapid increase of the drug concentration in plasma of an alkylendioxybenzene derivative represented by the general formula (I):



(wherein m represents an integer of 2 to 5, and n represents an integer 1 to 3)

or an acid addition salt thereof, and allows for duration of the drug concentration in plasma.

### Brief Description of Drawings

FIG. 1 shows the results of a dissolution test of the composition obtained in Example 1.

FIG. 2 shows the results of a dissolution test of a conventional preparation obtained in Comparative example 1.

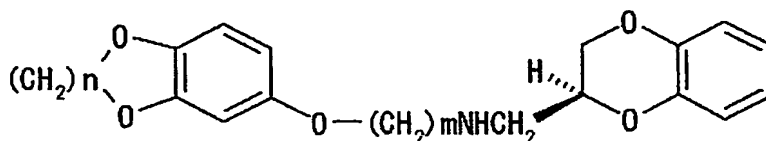
### Best Mode for Carrying Out the Invention

The present invention is as follows:

- (1) A composition for oral administration containing an alkylenedioxybenzene derivative represented by the general formula (I) or an acid addition salt thereof and a matrix material and/or a coating material.
- (2) The composition described in the above (1), wherein each of the material and the coating material is at least one kind selected from a synthetic polymer and waxes.
- (3) A composition for oral administration, wherein an alkylenedioxybenzene derivative represented by the general formula (I) or an addition salt thereof is dispersed in a matrix containing a synthetic polymer and/or waxes.
- (4) A composition for oral administration, characterized in that a composition containing an alkylenedioxybenzene derivative represented by the general formula (I) or an acid addition salt thereof and a synthetic polymer and/or waxes is coated with a coating agent containing a synthetic polymer.
- (5) A composition for oral administration containing an alkylenedioxybenzene derivative represented by the general formula (I) or an acid addition salt thereof in a matrix containing waxes and an excipient.
- (6) A composition for oral administration, wherein a base granule containing an alkylenedioxybenzene derivative represented by the general formula (I) or an acid addition salt thereof dispersed in a matrix containing waxes and an excipient is coated with an enteric film.
- (7) The composition for oral administration described in the above (6), wherein an amount of waxes is 5 to 70% by weight relative to the base granule.
- (8) The composition for oral administration described in any one of the above (1) to (6), wherein the synthetic polymer is at least one kind selected from polyvinyl type, acrylic acid or acrylic acid ester type and cellulose type, and the waxes are at least one kind selected from shellac, gelatin, hydrogenated oil, higher fatty acid and esters thereof, higher aliphatic alcohol, and natural and synthetic waxes.
- (9) A capsule containing an alkylenedioxybenzene derivative or an acid addition salt thereof, comprising the composition for oral administration described in the above

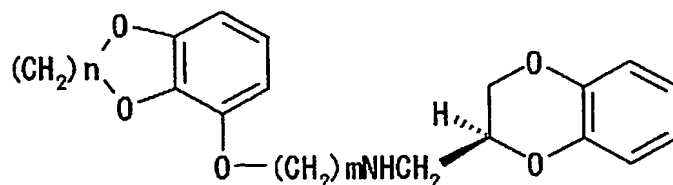
- (1) filled therein.
- (10) A process for preparing a composition for oral administration, comprising kneading an alkylenedioxybenzene derivative represented by the general formula (I) or an acid addition salt thereof, waxes and an excipient to obtain a granule, and coating the granule with an enteric film.
- (11) A composition for oral administration, wherein a pharmaceutically active substance is an alkylenedioxybenzene derivative represented by the general formula (I) or an acid addition salt thereof, and a time for releasing at least 80% of a content of the pharmaceutically active substance is 2 to 24 hours when tested at 100 rotations per minute using 900 ml of a hydrochloric acid/trisodium phosphate buffer (pH 6.8) according to a basket method (USP dissolution test method first method).
- (12) The composition for oral administration according to any one of the above (1) to (11), wherein the alkylenedioxybenzene derivative or the acid addition salt thereof is 5-[3-[[[(2S)-1,4-benzodioxan-2-ylmethyl]amino]propoxy]-1,3-benzodioxole hydrochloride.

Examples of the alkylenedioxybenzene derivative represented by the general formula (I) include compounds represented by Table 1 and Table 2.



[Table 1]

Compound No.	M	n
1	3	1
2	3	2
3	3	3
4	4	1
5	4	2
6	4	3
7	5	1
8	5	2
9	5	3
10	2	1
11	2	2
12	2	3



[Table 2]

Compound No.	M	n
13	3	1
14	3	2
15	3	3
16	4	1
17	4	2
18	4	3
19	5	1
20	5	2
21	5	3
22	2	1
23	2	2
24	2	3

Of the compounds represented by the general formula (I), a compound of Compound No. 1 is preferable. Examples of an acid in the acid addition salt of the alkylenedioxybenzene derivative include inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and nitric acid, and organic acids such as acetic acid, succinic acid, adipic acid, propionic acid, tartaric acid, fumaric acid, maleic acid, oxalic acid, citric acid, benzoic acid, toluenesulfonic acid and methanesulfonic acid. The alkylenedioxybenzene derivative of the general formula (I) or an acid addition salt thereof can be synthesized by the method described in US Patent 5,168,099.

Since the present invention is a dosage form that at least 80% of a content of a drug is released in 2 to 24 hours in a USP dissolution test method first method, it can be applied to all kinds of regulated-release compositions which are known in the art.

Further, the present invention provides a composition for oral administration comprising the following (a) and (b).

- (a) An alkylenedioxybenzene derivative of the general formula (I) or an acid addition

salt thereof.

- (b) At least one release rate-controlling substances having the effects showing the following (1) and/or (2) by administering the composition to a patient:
- (1) a time to a maximum plasma concentration ( $T_{max}$ ) of the alkylendioxybenzene derivative of the general formula (I) or the acid addition salt thereof ranging from 1.5 to 4.5 hours following administration; and
  - (2)  $C_{max}$  in plasma, of the alkylendioxybenzene derivative of the general formula (I) or the acid addition salt thereof is 100 to 300 ng/ml.

A matrix material and a coating material used may be any materials as far as they prevent permeation of water into a composition, and can control a desired releasing rate of a drug, and examples thereof include a synthetic polymer and waxes. It is preferable that amounts of a synthetic polymer and waxes to be used are 5 to 70% by weight, preferably 20 to 50% by weight relative to a base granule or a base tablet.

Preferable examples of the synthetic polymer include polyvinyl type (polyvinylalcohol, polyvinylpyrrolidone etc.), acrylic acid or acrylic acid ester type (polymer of methyl methacrylate or copolymer of acryl monomer, e.g. methacrylic acid copolymer LD, methacrylic acid copolymer L, methacrylic acid copolymer S, aminoalkyl methacrylate copolymer RS etc.), and cellulose type (biopolymer or degenerated biopolymer of cellulose, e.g. ethylcellulose, cellulose acetate phthalate, hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, sodium carboxymethylcellulose etc.).

Examples of the waxes include shellac, gelatin, hydrogenated oil (fat obtained by adding hydrogen to vegetable or animal fatty oil, such as hydrogenated beef tallow, hydrogenated castor oil, hydrogenated cottonseed oil, hydrogenated soybean oil etc.), higher fatty acid and esters thereof (stearic acid, palmitic acid, aluminium monostearate, glyceryl mono- or dipalmitate, glyceryl mono-, di- or tristearate etc.), higher aliphatic alcohol (cetyl alcohol, stearyl alcohol, myristyl alcohol, 12-hydroxystearyl alcohol etc.), and natural and synthetic waxes (beewax, Japan wax, carnauba wax, paraffin wax, whale wax, synthetic wax etc.). Among them, hydrogenated oil is preferable.

These synthetic polymers and waxes may be used alone or in combination.

In the composition of the invention, various additives which are normally used in the art such as excipient, binder, lubricant and aggregation preventing agent can be used. Examples of the excipient include sugars (white sugar, lactose, glucose, maltose etc.), sugar alcohol (mannitol, sorbitol, xylitol etc.), starch, crystalline cellulose, calcium



phosphate and calcium sulfate. Examples of the binder include polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, polyvinylpyrrolidone, dextrin, hydroxyethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, macrogols, gum arabic, gelatin, agar and starch. In addition, examples of the lubricant and aggregation preventing agent include talc, magnesium stearate, calcium stearate, and polyethylene glycols. These can be used by appropriately combining them.

A granule can be prepared by adding a synthetic polymer or waxes to a drug and, if necessary, adding an excipient such as lactose and mannitol, adding a solvent, and kneading them to be granulated and dried (Process 1). Since, in the thus obtained granule, the drug is dispersed in a matrix containing the synthetic polymer or waxes, the drug is gradually released in water or in a gastrointestinal tract.

The granule in the present invention can be also obtained by adding an excipient such as lactose and mannitol to a drug, adding small amounts of a binder and a solvent, and granulating to prepare a normal granule which is not dispersed into a matrix, and coating this granule with an enteric film. Also in this case, the drug is gradually released in an intestinal tract. These granulation and coating can be performed by apparatuses which are conventionally used.

pH in stomach is usually 1.8 to 4.5 in a healthy subject, and in view of dependency of the solubility of the alkylendioxybenzene derivative on a pH, stable drug release in stomach can not be desired. In view of that a pH variation in intestine is 6.5 to 7.5, after passed through stomach having a great pH variation due to enteric film coating, stable release becomes possible in an intestinal tract. Therefore, it is also possible to coat the composition obtained in the aforementioned process 1 with an enteric film.

A preferable aspect of the present invention is to mix an alkylendioxybenzene derivative and a synthetic polymer and/or waxes, and an additive, extrude and granulate the mixture, and coat the resulting granule with an enteric film. Further, by filling the thus obtained regulated/prolonged release composition into a capsule, a capsule agent can be provided.

As the enteric film, the aforementioned synthetic polymer and waxes can be used. A method of coating with an enteric film is not particularly limited. Any of aqueous and non-aqueous systems which are conventionally used in this field can be applied, and application can be performed by methods which are conventionally used in the pharmacy techniques such as spray coating in a fluidized bed coating method, a rolling flowing type coating method, and the like.

A coating rate of the enteric film is different depending on a kind of a drug or film and, in each case, the rate may be appropriately regulated. It is desirable to use a film such that a coating amount becomes 5 to 50 W/W % relative to a drug. Preferably, a film is used at an amount of 20 to 40% by weight relative to a granule, at an amount of 5 to 30% by weight relative to a tablet.

### Examples

The present invention will be explained in more detail below by way of Examples, but the present invention is not limited thereto.

In the following Examples and Experimental examples, MKC-242 indicates 5-[3-[[[(2S)-1,4-benzodioxan-2-ylmethyl]amino]propoxy]-1,3-benzodioxole hydrochloride (hydrochloride of a compound of Compound No. 1).

#### Example 1

300 g of MKC-242, 1500 g of D-mannitol (trade name: D-Mannitol, Kao Corporation), 900 g of hydrogenated oil (trade name: Lubri Wax 101, Kawaken Fine Chemicals. Co., Ltd.), 150 g of Microcrystalline cellulose (trade name: Avicel PH101, Asahi Chemical Industry Co., Ltd.) and 150 g of hydroxypropylcellulose (trade name: HPC-L, Nippon Soda Co., Ltd.) are placed into a stirring and mixing granulator (FS-GS-25J type, Fukae Kogyo) to mix them. Then, 390 g of water is added while mixing, followed by kneading. This kneaded material is granulated by extruding with a cylindrical granulator (HG-200 type, Hata Tekkosho). A size of the resulting extruded granule is adjusted with Malmerizer (Q-230 type, Dalton Corporation), and the granule is placed into a fluidized bed granulating dryer (FLO-5M type, Freund Industrial Co., Ltd.) and is dried with a warm window at 70°C.

Then, 1000 g of the resulting granule is placed into a rolling fluidized bed granulating dryer (MP-01 type, Powrex Corporation), and a coating solution obtained by adding 555 g of methacrylic acid copolymer LD (trade name: Eudragit L30D-55, Degussa), 17 g of triethyl citrate (trade name: Citroflex SC60, Morimura Bros., Inc.), 17 g of talc (Hayashi Kasei Inc.) and 555 g of water is sprayed thereto while blowing a warm wind at 60°C therein, to obtain a granule in which drug release is regulated.

#### Example 2

300 g of MKC-242, 1500 g of D-mannitol (trade name: D-Mannitol, Kao Corporation), 900 g of carnauba wax (trade name: Polishing wax 103, Kawaken Fine Chemicals. Co., Ltd.), 150 g of Microcrystalline cellulose (trade name: Avicel PH101, Asahi Chemical Industry Co., Ltd.) and 150 g of hydroxypropylcellulose (trade name

HPC-L, Nippon Soda Co., Ltd.) are placed into a stirring and mixing granulator (FS-GS-25J type, Fukae Kogyo) to mix them. Then, 390 g of water is added while mixing, followed by kneading. This kneaded material is granulated by extruding with a cylindrical granulator (HG-200 type, Hata Tekkosho). A size of the resulting extruded granule is adjusted with Malmerizer (Q-230-type, Dalton Corporation), and the granule is placed into a fluidized bed granulating dryer (FLO-5M type, Freund Industrial Co., Ltd.) and is dried with a warm wind at 70°C.

Then, 1000 g of the resulting granule is placed into a rolling fluidized bed granulating dryer (MP-01 type, Powrex Corporation), and a coating solution obtained by adding 555 g of methacrylic acid copolymer (LD (trade name: Eudragit L30D-55, Degussa), 17 g of triethyl citrate (trade name: Citroflex SC60, Morimura Bros., Inc.), 17 g of talc (Hayashi Kasei Inc.) and 555 g of water is sprayed thereto while blowing a warm wind at 60°C therein, to obtain a granule in which drug release is regulated.

### Example 3

300 g of MKC-242, 1500 g of D-mannitol (trade name: D-Mannitol, Kao Corporation), 900 g of stearic acid (trade name: Stearic Acid, Kao Corporation), 150 g of Microcrystalline cellulose (trade name: Avicel PH101, Asahi Chemical Industry Co., Ltd.) and 150 g of hydroxypropylcellulose (trade name: HPC-L, Nippon Soda Co., Ltd.) are placed into a stirring and mixing granulator (FS-GS-25J type, Fukae Kogyo) to mix them. Then, 390 g of water is added while mixing, followed by kneading. This kneaded material is granulated by extruding with a cylindrical granulator (HG-200 type, Hata Tekkosho). A size of the resulting extruded granule is adjusted with Malmerizer (Q-230 type, Dalton Corporation), and the granule is placed into a fluidized bed granulating dryer (FLO-5M type, Freund Industrial Co., Ltd.) and dried with a warm wind at 70°C.

Then, 1000 g of the resulting granule is placed into a rolling fluidized bed granulating dryer (MP-01 type, Powrex Corporation), and a coating solution obtained by adding 555 g of methacrylic acid copolymer LD (trade name: Eudragit L30D-55, Degussa), 17 g of triethyl citrate (trade name: Citroflex SC60, Morimura Bros., Inc.), 17 g of talc (Hayashi Kasei Inc.) and 555 g of water is sprayed thereto while blowing a warm wind at 60°C therein, to obtain a granule in which drug release is regulated.

### Example 4

300 g of MKC-242, 1800 g of D-mannitol (trade name: D-Mannitol, Kao Corporation), 600 g of hydrogenated oil (trade name: Lovely Wax 101, Kawaken Fine Chemicals. Co., Ltd.), 150 g of Microcrystalline cellulose (trade name: Avicel PH101, Asahi Chemical Industry Co., Ltd.) and 150 g of hydroxypropylcellulose (trade name:

HPC-L, Nippon Soda Co., Ltd.) are placed into a stirring and mixing granulator (FS-GS-25J type, Fukae Kogyo). Then, 390 g of water is added while mixing, followed by kneading. This kneaded material is granulated by extruding with a cylindrical granulator (HG-200 type, Hata Tekkosho). A size of the resulting extruded granule is adjusted with Malmerizer (Q-230 type, Dalton Corporation), and the granule is placed into a fluidized bed granulating dryer (FLO-5M type, Freund Industrial Co., Ltd.) and is dried with a warm wind at 70°C.

Then, 1000 g of the resulting granule is placed into a rolling fluidized bed granulating dryer (MP-01 type, Powrex Corporation), and a coating solution obtained by adding 555 g of methacrylic acid copolymer LD (trade name: Eudragit L30D-55, Degussa), 17 g of triethyl citrate (trade name: Citroflex SC60, Morimura Bros., Inc.), 17 g of talc (Hayashi Kasei Inc.) and 555 g of water is sprayed thereto while blowing a warm wind at 60°C therein, to obtain a granule in which drug release is regulated.

#### **Comparative example 1 (conventional preparation)**

40 g of MKC-242, 4656 g of D-mannitol (trade name: D-Mannitol, Kao Corporation), and 540 g of sodium carboxymethylstarch (trade name: Primojel, Matsutani Chemical Industry Co., Ltd.) are placed into a stirring and mixing granulator (FS-GS-25J of type, Fukae Kogyo) to mix them. Then, the mixed powder is granulated using a 6% dissolving solution containing hydroxypropylcellulose (trade name: HPC-L, Nippon Soda Co. Ltd.) and water by a fluidized bed granulator (FLO-5M, Freund Industrial Co., Ltd.), to obtain a granule. A size of this resulting granulated granule is adjusted with a size adjuster (ND-10, Okada Seiko). Further, 5255 g of this size-adjusted powder and 55 g of magnesium stearate (trade name: Magnesium Stearate, Nitto Kasei Co., Ltd.) are mixed with a V-type mixer (SVM-50, Meiwa Co., Ltd.) to obtain a tablet bulk powder. This tablet bulk powder is made tablet with a tableting machine (AQUA, Kikusui Seisakusho Ltd.) to obtain a fast-releasing tablet.

#### **Experimental Example 1: Releasing test**

Regarding the granule obtained in Example 1, a releasing pattern was compared at the condition of 100 rpm and 37°C by a basket method (USP dissolution test method first method) using a 0.1 mol/L hydrochloric acid solution (pH 1.2) and a hydrochloric acid/trisodium phosphate buffer (pH 6.8).

The results are shown in FIG. 1. In the granule obtained in Example 1, release of a drug hardly occurs in the 0.1 mol/L hydrochloric acid solution (pH 1.2) even when two hours passed, and it can be seen that the acid resistance is considerably retained. In addition, in the hydrochloric acid/trisodium phosphate buffer, a 10 hour-type releasing time profile is shown and, in a dissolution test, it was confirmed that a composition for

oral administration having a controlled drug releasing rate was obtained.

On the other hand, regarding the conventional preparation obtained in Comparative example 1, a releasing pattern was studied at the condition of 50 rpm and 37°C by a paddling method using Japanese Pharmacopoeia first solution (pH 1.2) and Japanese Pharmacopoeia second solution (pH 6.8). As a result, as shown in FIG. 2, approximate 100% was dissolved out in one hour in the conventional preparation.

### Experimental example 2

Absorption in a living body and drug acceptability of the granule containing 10mg of MKC-242 obtained in Example 1 were tested in 6 healthy subjects. As a reference, the conventional preparation (Comparative example 1) having the same drug dose was used.

**Table 3**

Change of drug concentration in blood Unit : ng/ml

Hour (hr)	Example 1	Comparative Example 1
Predose	0	0
1	2.4	335.3
2	51.1	255.3
4	178.4	101.9
6	79.5	36.9
8	50.2	20.3
12	30.1	7.9
24	10.1	1.2

**Table 4**

Pharmacokinetic Parameters obtained from unchanged case concentration in plasma (n = 6)

Dosage form	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)	T <sub>1/2</sub> (hr)	AUC (ng*hr/mL)	Adverse events
Example 1	202.4 ? 71.7	3.4 ? 0.7	11.9 ? 12.6	993 ? 242	0/6
Comparative Example 1	431.8 ? 176.6	1.1 ? 0.6	2.9 ? 1.1	1110 ? 430	5/6

As seen from Table 3 and Table 4, these two kinds of preparations showed the remarkably different plasma concentration profile. In the regulated-releasing composition of Example 1, the blood concentration is increased at a low absorption rate after around 1 hour lag time as compared with the conventional preparation, and the

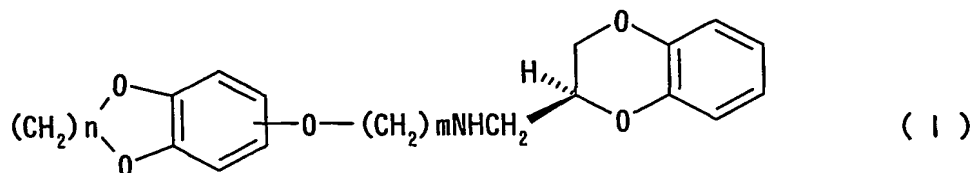
maximum blood concentration  $C_{\max}$  is considerably low as compared with the fast-releasing preparation. In the preparation of Example 1, symptoms such as dizziness was not detected, and the drug acceptability was improved. Further, a half-life  $T_{1/2}$  of the drug was extended from 3 hours to 20 hours, demonstrating that the drug concentration in plasma is maintained for a long period of time. In addition, since a scatter of AUC is small, stable drug release is performed in a living body, suggesting the effect of the enteric film.

### **Industrial Applicability**

The present invention provides a safe and useful pharmaceutical preparation for oral administration which can maintain the drug concentration in plasma for a long period of time, and the composition having the stable drug releasing property in a living body was obtained. Moreover, a drug containing an alkylendioxybenzene derivative such as MKC-242 and the like can be administered once to twice per day, and a burden of a patient can be alleviated.

## CLAIMS

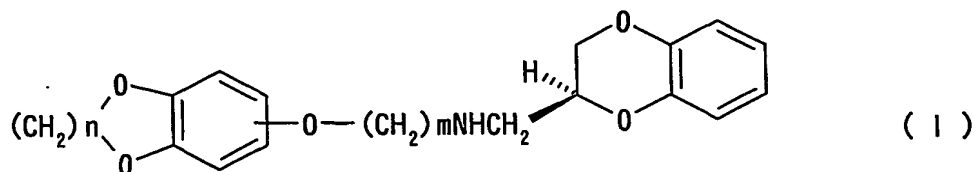
1. A composition for oral administration containing an alkylenedioxybenzene derivative represented by the general formula (I):



(wherein m represents an integer of 2 to 5, and n represents an integer of 1 to 3)  
or an acid addition salt thereof and a matrix material and/or a coating material.

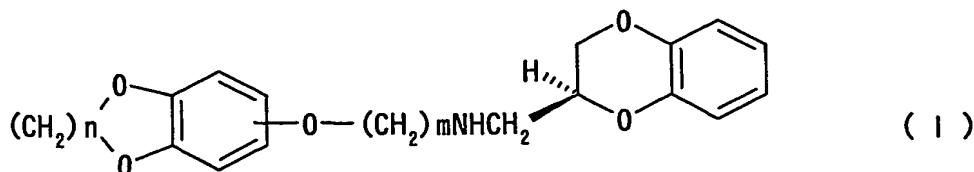
2. The composition according to claim 1, wherein each of the matrix material and the coating material is at least one kind selected from a synthetic polymer and waxes.

3. A composition for oral administration, wherein an alkylenedioxybenzene derivative represented by the general formula (I):



(wherein m represents an integer of 2 to 5, and n represents an integer of 1 to 3)  
or an acid addition salt thereof is dispersed in a matrix containing a synthetic polymer and/or waxes.

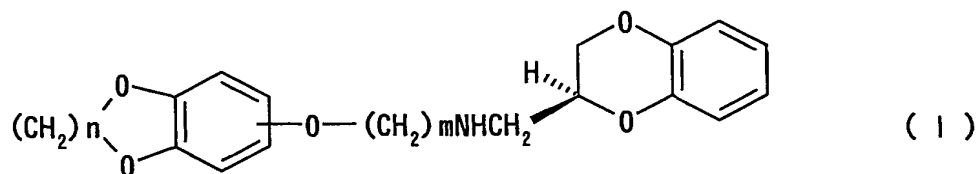
4. A composition for oral administration, characterized in that a composition containing an alkylenedioxybenzene derivative represented by the general formula (I):



(wherein m represents an integer of 2 to 5, and n represents an integer of 1 to 3)  
or an acid addition salt thereof and a synthetic polymer and/or waxes is coated with a

coating agent containing a synthetic polymer.

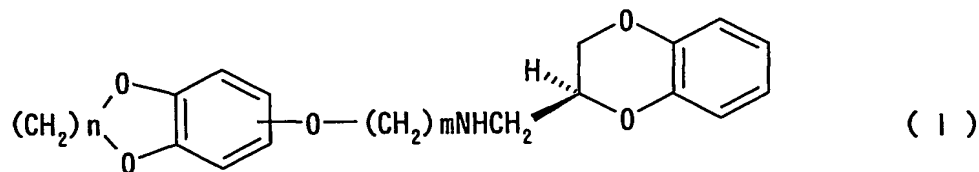
5. A composition for oral administration containing an alkylenedioxybenzene derivative represented by the general formula (I):



(wherein m represents an integer of 2 to 5, and n represents an integer of 1 to 3)

or an acid addition salt thereof in a matrix containing waxes and an excipient.

6. A composition for oral administration, wherein a base granule containing an alkylenedioxybenzene derivative represented by the general formula (I):



(wherein m represents an integer of 2 to 5, and n represents an integer of 1 to 3)

or an acid addition salt dispersed in a matrix containing waxes and an excipient is coated with an enteric film.

7. The composition for oral administration according to claim 6, wherein an amount of waxes is 5 to 70% by weight relative to the base granule.

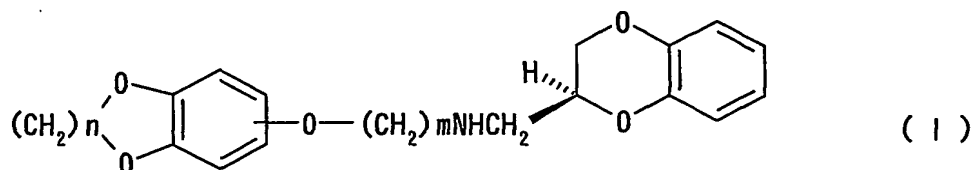
8. The composition for oral administration according to any one of claims 1 to 6, wherein the synthetic polymer is at least one kind selected from polyvinyl type, acrylic acid or acrylic acid ester type and cellulose type, and the waxes are at least one kind selected from shellac, gelatin, hydrogenated oil, higher fatty acid and esters thereof, higher aliphatic alcohol, and natural and synthetic waxes.

9. A capsule containing an alkylenedioxybenzene derivative or an acid addition salt thereof, comprising the composition for oral administration according to claim 1 filled



therein.

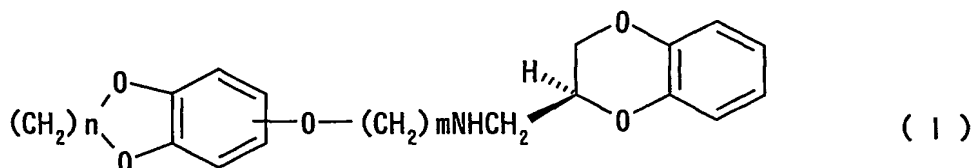
10. A process for preparing a composition for oral administration, comprising kneading an alkylendioxybenzene derivative represented by the general formula (I):



(wherein m represents an integer of 2 to 5, and n represents an integer of 1 to 3)

or an acid addition salt thereof, waxes and an excipient to obtain a granule, and coating the granule with an enteric film.

11. A composition for oral administration, wherein a pharmaceutically active substance is an alkylendioxybenzene derivative represented by general formula (I):



(wherein m represents an integer of 2 to 5, and n represents an integer of 1 to 3)

or an acid addition salt thereof, and a time for releasing at least 80% of a content of the pharmaceutically active substance is 2 to 24 hours when tested at 100 rotations per minute using 900 ml of a hydrochloric acid/trisodium phosphate buffer (pH 6.8) as a test solution according to a basket method (USP dissolution test first method).

12. The composition for oral administration according to any one of claims 1 to 11, wherein the alkylendioxybenzene derivative or the acid addition salt thereof is 5-[3-[[[(2S)-1,4-benzodioxan-2-ylmethyl]amino]propoxy]-1,3-benzodioxole hydrochloride.

1/1

Fig.1

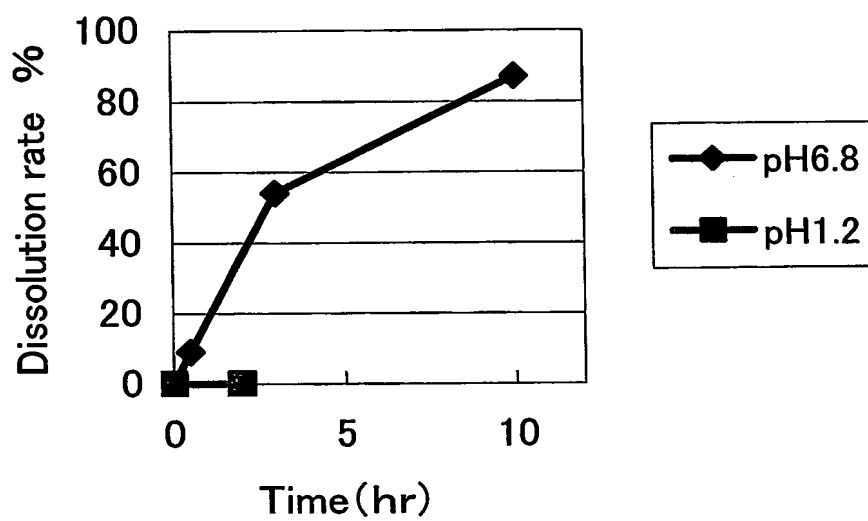
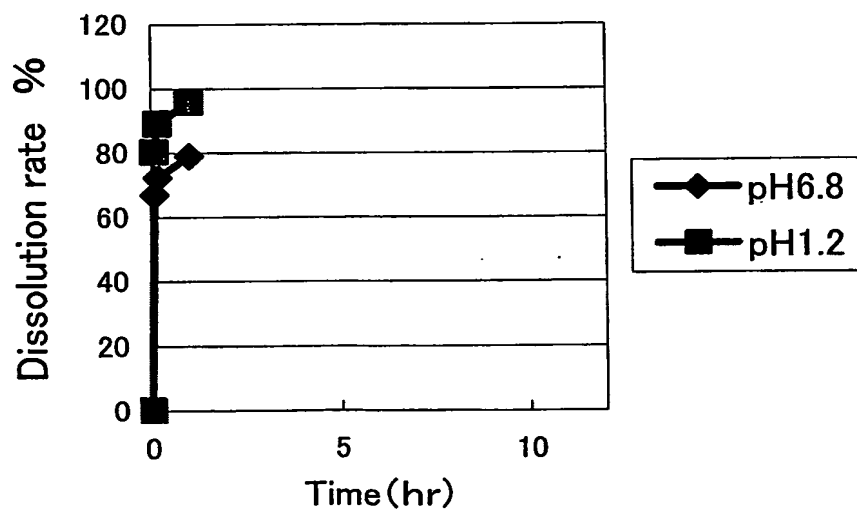


Fig.2



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 2004/005864

## A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl.<sup>7</sup> A61K31/36, 47/10, 47/12, 47/14, 47/32, 47/34 (continue to the extra sheet)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl.<sup>7</sup> A61K31/00-31/36, 47/00-47/44, 9/00-9/52, A61P1/00-43/00, C07D407/00-407/14

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
 Japanese Utility Model Gazette 1922-1996, Japanese Publication of Unexamined Utility Model Applications 1971-2004, Japanese Registered Utility Model Gazette 1994-2004, Japanese Gazette Containing the Utility Model 1996-2004

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAPLUS (STN), WPI (DIALOG)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/08675 A1 (MITSUBISHI CHEMICAL CORPORATION) 1999.02.25, example, lines 3-19, page 9, & EP 1010425 A1 & US 6596759 B2 & US 2002/0091152 A1 & EP 1010425 B1	1-12
Y	JP 11-35461 A (MITSUBISHI CHEMICAL CORPORATION) 1999.02.09, example, [0012], [0020], [0021], & EP 884049 A1 & CA 2238065 A & US 6160005 A & EP 884049 B1	1-12
Y	US 5168099 A (MITSUBISHI KASEI CORPORATION) 1992.12.01, examples, line 64, column 3 to line 2, column 4, & JP 3-264528 A & EP 446921 A1 & CA 2038025 A & US 5234948 A & EP 446921 B1	1-12



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

02.08.2004

Date of mailing of the international search report

24. 8. 2004

Name and mailing address of the ISA/JP

Japan Patent Office

3-4-3, Kasumigaseki, Chiyoda-ku, Tokyo 100-8915, Japan

Authorized officer

Hidenori ARAKI

4C

9736

Telephone No. +81-3-3581-1101 Ext. 3450

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2004/005864

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 4-288072 A (MITSUBISHI KASEI CORPORATION) 1992.10.13, examples, [0014] (Family: none)	1-12
Y	JP 5-132416 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 1993.05.28, claims, examples, [0002]-[0003], [0037], [0054], [0059], [0066], & EP 514008 A1 & CA 2066384 A & EP 514008 B1 & US 5576025 A & US 5731006 A & KR 217165 B1 & JP 2001-354550 A & JP 2001-354593 A & US 6368635 B1 & US 2002/0142041 A1	1-12
Y	JP 7-76517 A (YAMANOUCHI PHARM. CO., LTD.) 1995.03.20, whole document (Family: none)	1-12
A	JP 2001-500150 A (SMITHKLINE BEECHAM PLC) 2001.01.09, & WO 98/10762 A2 & AU 9741288 A & NZ 334268 A & NO 9901194 A & ZA 9708133 A & EP 929301 A2 & CZ 9900832 A3 & BR 97117334 A & CN 1235544 A & HU 9904401 A2 & CN 1446535 A & MX 9902404 A1 & KR 2000036039 A & US 2001/0003588 A1 & US 2002/0031550 A1 & US 6468560 B2 & US 2003/0157169 A1	1-12
A	JP 2-223533 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 1990.09.05, & EP 368247 A1 & CA 2002363 A & DK 8905553 A & AU 8944437 A & ZA 8908470 A & AU 9338561 A & EP 368247 B1 & US 5399357 A & US 5593690 A	1-12

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2004/005864

Continuation of "CLASSIFICATION OF SUBJECT MATTER"

Int.C17 A61K47/38,47/42,47/44,9/14,9/16,9/48,9/52,

A61P25/22,25/24 // C07D407/12